The Requirement for Restriction continues to be traversed.

Claims 1-20 have been subject to a requirement for restriction. While Claims 1-6 have been elected and are presently under consideration, Applicants reaffirm their right and intention to pursue non-elected Claims 7-20.

The Invention possesses utility

Claims 1-6 have been rejected under 35 U.S.C. §101 as purportedly lacking a specific or well-established utility. Applicants respectfully traverse the Examiner's rejections in this regard for the following reasons.

By identifying molecularly the gene defined by the *gro-1(e2400)* mutation, Applicants have shown that manipulating the gene coding for IPT (*gro-1)* produces effects on physiological rates. Specifically, the present invention provides a *gro-1* gene which has a function at the level of cellular physiology involved in developmental rate and longevity. The *gro-1* gene is located within an operon, and *gro-1* mutants have a longer life and an altered cellular metabolism relative to the wild-type, as evidenced at page 9, lines 12-18, and Figs. 1A and 1B.

In addition, *gro-1, gop-1, gop-2, gop-3*, and *hap-1* have been identified in a single operon, thus indicating that they are co-expressed. Applicants have shown by RT-PCR (using primers of which sequences are provided in the description of the invention) that these five open reading frames were transcribed as part of an operon. Specifically, Applicants have shown experimentally that *gro-1, gop-2, gop-3,* and *hap-1* are all SL2-transpliced, and that *gop-1* is not transpliced (see Figs. 4A-4B), thus establishing the fact that they occur in an operon and are

transcriptionally co-expressed.

According to this finding, Applicants respectfully submit that a person of skill in the art would realize the benefit of using the *gro-1* gene in other organisms to influence developmental rate and longevity. In the benefit of the teachings of the present disclosure and invention, a person of skill in the art could not otherwise predict that this gene would be useful as a target to manipulate physiological rates in an animal. By identifying a target for manipulating physiological rates in an animal, the present invention provides a specific utility in that the developmental rate and longevity of an animal may be altered.

Further, the Examiner asserts that while the specification teaches of a human EST that can be used to construct the polynucleotide having similarity to the *C. elegans gro-1* gene, there is insufficient evidence that this polynucleotide is expressed as a protein in humans. As a result, it is the Examiner's opinion that a person of skill in the art would not be able to predict if the human polynucleotide having homology to the *gro-1* gene was in fact translated into the human *GRO-1* protein.

Once again, Applicants respectfully traverse the Examiner's arguments on such basis for the following reasons.

First, the *gro-1* gene exists in all eukaryotic organisms for which the sequence of the genome is known, as well as in many others, and has thus been evolutionarily conserved (Stanford *et al.*, 2000, a copy of which is enclosed as Exhibit I). In addition, the *gro-1* encoded enzyme, tRNA isopentenyl transferase, is encoded by a single gene in all studied metazoans, which indicates that the genes of the different species are orthologues, and thus must have a

similar function.

Secondly, the human *gro-1* gene is indeed expressed. Not only are EST for *hgro-1* available, indicating that the gene is transcribed, but also the mRNA resulting from transcription of the *hgro-1* gene is translated *in vivo*. Indeed, Golovko *et al.* (2000) (herein provided as Exhibit II) report that transformation of human *MOD-5/gro-1* cDNA into a yeast mutant for *MOD5* can functionally complement the lack of *MOD5* gene function, including restoring the isopentenyl-adenosine modification of tRNAs. That the enzymatic activity is present indicates that the cDNA corresponding to the *hgro-1* gene is translated into protein *in vivo* and that the protein has indeed that particular enzymatic activity.

Thirdly, that the level of *hgro-1* transcription and translation may be affected by environmental and other factors does not affect the basic conclusion that it is an active gene. Indeed, isopentenylated tRNA are found in mammalian, including human cells.

It is the Examiner's further opinion that the present application does not provide objective evidence in support of the claim that the hypothetical human *GRO* protein mediates the development in aging or any other disease process in humans. Once again, Applicants respectfully disagree with the Examiner's assertions in this regard.

Upon appreciation of all aspects of the utility of the specific genes located in the *gro-1* operon in the nematode and mutants thereof as taught in the present application, Applicants respectfully submit that it is only a matter of adapting, without undue experimentation, what is described in the present application for the nematode, with homologous sequences identified in other organisms according to methodologies known in the art.

As previously mentioned, *gro-1* is a highly conserved gene which encodes a protein whose enzymatic function has been conserved from yeast to humans (Golovko *et al.*, 2000). As a mutation that alters (*e.g.* reduces) the activity of the gene *gro-1* of the metazoan, *C. elegans*, and affects physiological rates and life span, similar effects on physiological rates will exist in the human when the level of gene function and/or protein activity is altered (*e.g.* reduces). It has been found to be the rule that when proteins are carrying out similar biochemical functions, they have similar effects on the organism. This is a general finding, but numerous examples of functional conservation exist, particularly from nematode to human. One of them is the conservation of function between the human *Bcl-2* and the *C. elegans ced-9* genes in regulation of apoptosis. Apoptosis is an evolutionarily conserved process by which a cell destroys itself. The specialized machinery regulating and executing the apoptotic events is remarkably conserved between nematodes and humans. Three worm apoptosis components have been identified by genetic analysis in *C. elegans*. One gene, *ced-9*, is essential to prevent cell death The predicted encoded nematode protein *CED-9* is similar to the human proto-oncogene protein *Bcl-2*. A number of experiments have demonstrated that human *Bcl-2* and nematode *CED-9* function in very similar ways. First, human *Bcl-2* can function in the nematode, reducing the number of cell death. Secondly, human *Bcl-2* expression can substitute for *ced-9* function rescuing the abnormal deaths of *ced-9* mutants. Thirdly, co-expression of both *Bcl-2* and *CED-9* does not protect any better than expression of either protein itself. This suggests that the effects of *Bcl-2* and *CED-9* are not additive and that they function by similar or identical mechanism. Finally, the function of both *Bcl-2* and *CED-9* is mediated by the same domains in the proteins, the *Bcl-2*

homology domains *BH1* and *BH2*.

In the particular case of *gro-1*, it is known that the function of this gene and the enzymatic activity of the protein have been conserved from yeast to human. In fact, Golovko *et al.* (2000) reported that the human *gro-1* gene, coding for the tRNA isopentenyl transferase, functions in the yeast *Saccharomyces cerevisiae*. They demonstrated that expression of the human gene in a yeast mutant lacking the endogeneous tRNA isopentenyl transferase *MOD5/gro-1* results in functional complementation, and restores the enzymatic activity in the yeast as isopentenyladenosine is reintroduced to tRNA.

Given that the function of *MOD-5/gro-1* has been conserved from yeast to human, including its precise biochemical role, this demonstrates that the phenotypic consequences observed in a nematode mutant for the function of the gene *gro-1* would also exist in humans if the function of this gene is altered.

Additional support for a specific asserted utility of the invention as claimed in Claims 1-6 is further detailed on page 4 of the present application, lines 11-23. Specifically, a method for the diagnosis and/or prognosis of cancer is provided, which includes determining that the human *gro-1* gene is altered. As such, alteration of the human *gro-1* gene is indicative of cancer since altered *gro-1* function leads to abnormal physiological rates. Accordingly, it would be clear to a person of skill in the art from the teachings of the present application that a *gro-1* gene may be used as a marker for disease and/or aging rate. Furthermore, the subject matter of Claims 1-6 of the present application finds further utility in an animal model of aging and cancer, wherein a gene homologous *gro-1* is knocked out of action.

In view of the preceding comments, Applicants respectfully submit that Claims 1-6 of the present application are supported by a specific asserted utility. That is, the present application identifies a specific utility for the claimed invention and provides sufficient disclosure concerning the same to make its utility apparent to a person of skill in the art. Reconsideration of the Examiner's rejections in this regard is respectfully requested.

The Invention is enabled

Claims 1-6 of the present application have also been rejected under 35 U.S.C. §112, paragraph 1, on the basis that the specification does not describe the claimed invention in such a way as to enable a person of skill in the art to make and/or use the invention. This rejection is traversed.

In conjunction with Applicants' comments as outlined hereinabove, Applicants further submit that the present application would sufficiently provide a person of skill in the art with the ability to practice the claimed invention without undue experimentation. As such, it would be clear to a person of skill in the art, having the teachings of the present application in hand, how to make and use the claimed invention.

Favorable reconsideration of the Examiner's rejections to the claims of the present application is herein respectfully requested.

Fees

No additional fees are believed to be necessitated by this response. However, should this be in error, authorization is hereby given to charge Deposit Account No. 11-1153 for any underpayment, or to credit any overpayments.

CONCLUSION

For the foregoing reasons, favorable consideration and entry of the foregoing Amendment, and reconsideration and allowance of the pending Claims are courteously solicited.

Respectfully submitted,

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ENCLOSURES: EXHIBITS I & II